

**Remarks**

Claims 1-15 are pending in the present application. Claim 15 has been withdrawn as drawn to non-elected subject matter. Applicants are cancelling non-elected claim 15 herein, without prejudice to prosecution of the canceled subject matter in a divisional application, the restriction requirement having been made final.

Claims 1-14 are rejected under 35 U.S.C. §103(a) as obvious over Mueller et al. in view of al-Hashimi et al. Mueller et al. is cited for teaching a method for determining the global fold of maltodextrin-binding protein by refining NMR analysis of the protein obtained from measurements in non-aligned medium using dipolar coupling restraints in partially aligned liquid crystal medium. The Office concedes that the reference does not teach measuring dipolar couplings in two different stages of partial alignment. al-Hashimi et al. is cited as teaching measuring in more than one medium. The reasoning for using this technique assertedly is that determining relative fragment orientations based on a single set of residual dipolar couplings is inherently hindered by the multi-valued nature of the angular dependence of the dipolar interaction, which is removed when measuring in two different aligned media. On the basis of these asserted teachings, the Office concludes that it would have been obvious to improve Mueller et al. by measuring in two different states of partial alignment as taught by al-Hashimi et al. The Office Action also mentions that any additional limitations in the dependent claims are of a minor nature and also would have been obvious since they represent only routine optimization of operative conditions.

Applicants traverse this rejection. In order to make out a prima facie case of obviousness against a claim, the Office must meet three criteria. M.P.E.P. §2143. First, the cited references, in combination, must teach or suggest each and every element of the rejected claim. Second, there must be motivation to modify or combine the references to achieve what is claimed. Third, there must be a reasonable expectation that if the references were combined and modified, such combination and modification would successfully result in the invention. Applicants submit that the Office cannot meet these criteria with respect to the claims of this application.

In summary, Mueller et al. used laborious methods which included obtaining distance data from (terminal) methyl protons. See abstract ("Distances to methyl protons, critical for the structure determination, comprised 77% of the long-range restraints."). In order to do this, atoms of the side chains must be assigned. So, the method requires one to assign not only the backbone, but the side chains as well. Even having done these steps, however, the methods results in resolution of only 2.2Å. Using backbone measurements only, the rmsd was 5.5Å, which is considered extremely poor resolution. In contrast, the method claimed here requires assignment of the backbone only, using angle measurements almost exclusively, and amide-amide distances which are assigned using backbone data and not side chain data. The side chains do not need to be assigned using the methods claimed here, greatly reducing the amount of work required to achieve the desired results.

The claims of this invention are directed to a method for determining the global fold of a peptidic molecule which is substituted on the backbone with  $^{13}\text{C}$ ,  $^{15}\text{N}$  or both; subjecting the

molecule to NMR analysis in a non-aligned medium; assigning it by computer based on the NMR analysis; measuring residual dipolar couplings for the molecule in two states of partial alignment; varying computationally by increments the  $\phi, \psi$  angles for a first amino acid of the molecule; minimizing the rigid-body orientation of the first amino acid and a second amino acid adjacent in the peptidic sequence to said first amino acid with respect to both tensor frames simultaneously; calculating the minimum difference between measured and calculated dipolar couplings for each of said first and second amino acids; deriving the  $\phi, \psi$  angles and orientation of the dipeptide fragment composed of these amino acids; and repeating these steps for each sequential dipeptide fragment to obtain a global fold. Mueller et al. do not teach or suggest these methods as claimed.

First, the structural information of Mueller et al. was obtained "based on 1943 NOEs, 48 hydrogen bonding, 555 dihedral angle and 940 dipolar coupling based restraints...." See page 198, column 2, lines 22-25. This large number of NOEs required for the Mueller et al. methods are determined using methyl protons from the side chains of amino acids and are "are particularly important in defining the orientation of this helix." To the contrary, the present methods as claimed do not require such laborious and time-consuming work because the data obtained from the claimed methods allows one to obtain the  $\phi, \psi$  angles using different measurement and data analytical methods instead, to obtain bond angles in the protein. Steps (f), (g), (h) and (i) of the method, for example, are not taught in Mueller et al. or even suggested. The inventive methods rely primarily on bond vector angles without having to resort to obtaining distance data from terminal methyl protons, which are required

when using the methods of Mueller et al. The Mueller et al. methods were able to predict backbone  $\phi, \psi$  angles only after correction using methyl proton data, see page 210, column 1, lines 19-22.

Furthermore, the limitations of step (a) are not suggested in Mueller et al., which teaches that side chain labeling needs to be performed. Therefore, the disclosures of Mueller et al. do not teach or suggest, at least steps (a) or (d)-(j) of claim 1. This reference alone, therefore, cannot be a proper basis for a rejection under 35 U.S.C. §103(a), as the Office concedes.

The al-Hashimi et al. reference discusses an experimental approach for combining two sets of residual dipolar coupling measurements of backbone  $^{15}\text{N}$ - $^1\text{H}$  data in two aligned media to obtain structural data for molecular fragments or secondary structural elements of a protein labeled with  $^{15}\text{N}$ . The authors of this reference did not achieve the global fold of the protein fragments they studied. Furthermore, they indicated that the approach they used should be supplemented with  $^1\text{H}$ - $^1\text{H}$  or  $^{13}\text{C}$ - $^1\text{H}$  residual dipolar coupling data if it were to be applied more broadly, i.e. to determine protein backbone structures for unknown proteins. See page 405, column 2, lines 39-46. These additional data are not part of the claimed method. These comments by the authors of al-Hashimi et al. lead the reader to the conclusion that merely measuring the backbone residual dipolar coupling data as they did, or as Mueller et al. did, would not result in the method obtained by applicants here.

The disclosures of al-Hashimi et al. do not teach or suggest the method claimed here and do not make up for the many deficiencies of the Mueller et al. reference. For example, al-Hashimi et al. do not teach or suggest at least the claim

elements (a), (b), (c) or (f)-(j) of claim 1. Therefore, the two cited references in combination lack any teaching or suggestion of more than one element required by the claim rejected here.

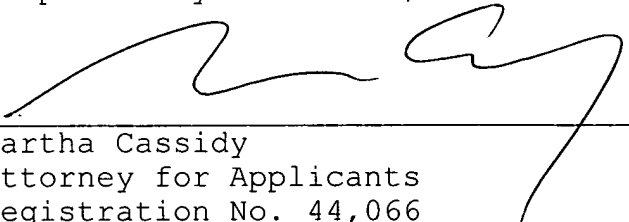
A prima facie case of obviousness is established only when the Office can demonstrate that the cited art teaches each and every claim limitation. The Office cannot meet this burden with respect to the claims of this application. In addition, there is nothing in either cited reference that would lead the skilled artisan to combine the teachings of the two cited references to attempt a method which involves steps (a)-(e) of claim 1. Nor is there any teaching or suggestion, or even the merest hint, that the reader should then modify these combined teachings to add the missing claim elements from steps (a) and (d)-(j), since no teaching or discussion even related to these steps has been cited in the Office Action. The Office therefore cannot meet the second necessary criterion for making out a prima facie case of obviousness. Applicants therefore submit that the rejection is not proper and should be withdrawn.

In addition, there is no reasonable expectation that the method of the invention as claimed would be successful based on the cited disclosures. Both references teach that a great deal of other information (including terminal methyl proton distances) would be required for the method to succeed. Therefore, the method which is claimed here is not only novel but would have been nonobvious at the effective filing date of this application.

For the reasons discussed above, Applicants request that the Office withdraw the rejection of claims 1-14 under 35 U.S.C. §103(a) and allow the claims to proceed to issue.

Respectfully submitted,

By



---

Martha Cassidy  
Attorney for Applicants  
Registration No. 44,066  
ROTHWELL, FIGG, ERNST & MANBECK, p.c.  
Suite 800, 1425 K Street, N.W.  
Washington, D.C. 20005  
Telephone: (202) 783-6040